CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Sept. 1995, p. 626–630 Vol. 2, No. 5
1071-412X/95/$04.00+0

Adenosine Deaminase Isoenzyme Levels in Patients with Human T-Cell Lymphotropic Virus Type 1 and Human Immunodeficiency Virus Type 1 Infections

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Received 17 March 1995/Returned for modification 25 April 1995/Accepted 15 June 1995

In serum, the enzyme adenosine deaminase (ADA) is known to be divided into two isoenzymes, ADA1 and ADA2, which have different molecular weights and kinetic properties. The present study investigated ADA isoenzyme levels in the sera of patients infected with retroviruses associated with adult T-cell leukemia (ATL), human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy (HAM), and AIDS. ADA isoenzyme activities were found to be significantly ($P < 0.001$) higher in the sera of patients with ATL, HAM, and AIDS than in the sera of healthy controls. In the case of the ADA subtypes in the sera of patients with ATL, ADA1 activity was significantly ($P < 0.001$) elevated in patients with the acute and lymphoma types of ATL compared with that in patients with the chronic and smoldering types of ATL. ADA2 activity was significantly elevated in the sera of patients with the acute, lymphoma, and chronic types of ATL ($P < 0.001$) compared with that in patients with smoldering ATL and HTLV-1 carriers. In the case of patients with human immunodeficiency virus type 1 (HIV-1) infection, ADA1 and ADA2 activities in the sera of patients with AIDS and HIV-1 antibody-positive individuals were significantly ($P < 0.001$) higher than those in the sera of HIV-1 antibody-negative individuals. A significant elevation in ADA2 activity was also seen in the sera of AIDS patients ($P < 0.01$) compared with that in the sera of HIV-1 antibody-positive individuals. These results suggest that the magnitude of elevation of ADA isoenzyme levels in serum correlated well with the clinical conditions of the patients with these diseases. Measurement of the activities of ADA isoenzymes may therefore provide an additional parameter for distinguishing the subtypes of ATL and may prove to be useful as prognostic and therapeutic monitors in diseases associated with HTLV-1 and HIV-1 infections.

An enzyme in the purine salvage pathway, adenosine deaminase (ADA; EC 3.5.4.4) is widely distributed in all human tissues. ADA is found to be present in higher concentrations in lymphoid tissues and is considered to play an important role in the differentiation and maturation of lymphoid cells (10). This relationship may have additional significance in T cells, since ADA is directly associated with the extracellular domain of CD26, which is defined as one of many T-cell activation antigens (8). The genetic deficiency of ADA results in severe combined immunodeficiency disease, and attention is focused on the correlation between immunodeficiency states and the ADA activity in erythrocytes, lymphocytes, and serum (5, 17).

ADA activity in humans is found to be associated with several different isoenzymes; ADA1 (40 kDa) is a monomer (designated as one catalytic unit) which can combine with a nonenzymatic 200-kDa, dimeric glycoprotein, designated as a combining protein (cp) (19). These ADA isoenzymes are denoted ADA1 (40 kDa) and ADA1+cp (280 kDa), and the levels of those isoenzymes are found to be clinically correlated with the severity of diseases in patients with severe combined immunodeficiency disease (23). Although these isoenzymes account for greater than 90% of the activity of ADA in human cells and tissue, an additional 110-kDa ADA isoenzyme, designated ADA2, has been reported in the spleen. ADA2 is a minor component of ADA activity in the spleen and the liver but a major component of the ADA activity in serum (25).

Adult T-cell leukemia (ATL) is a disease entity caused by human T-cell lymphotropic virus type 1 (HTLV-1) infection, found predominantly in the southwest region of Japan. The disease is subclassified into acute, chronic, smoldering, and lymphoma types on the basis of clinical features (24). HTLV-1-associated myelopathy (HAM) is also categorized as a new clinical entity found in Japan. The disease was found to be identical to tropical spastic paraparesis (20), which is known to have neurological and immunopathological characteristics (15). HTLV-1 is a retrovirus that causes ATL by infecting target cells, especially $CD4^+$ cells, subsequently transforming them into malignant cells, causing the clinical expression of leukemia. Human immunodeficiency virus type 1 (HIV-1), which is in the retrovirus family, also infects $CD4^+$ cells through CD4 molecules. HIV-1-infected individuals have significantly altered immunological behaviors and eventually develop AIDS.

Our preliminary results (30) and those of other investigators (14, 22) demonstrated that the levels of ADA in the sera of patients with HTLV-1 and HIV-1 infections are elevated. Our present study further defines the correlation between the elevated levels of ADA1 and/or ADA2 activities in serum and the clinical features of these diseases caused by retroviruses.

MATERIALS AND METHODS

Reagents. Adenosine, inosine, and polybrane were obtained from Sigma Chemical Co. (St. Louis, Mo.). Erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA)

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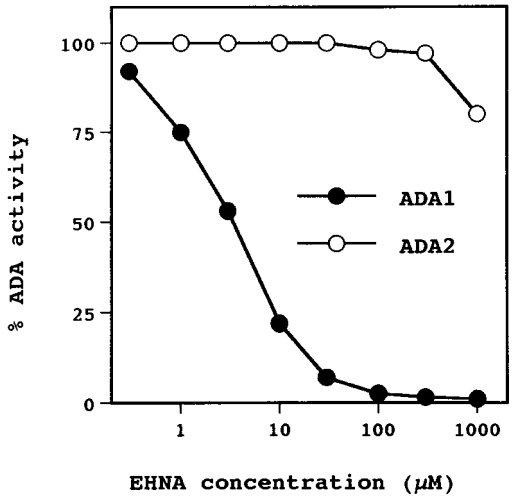

FIG. 1. Effect of EHNA on ADA1 and ADA2 activities. The activities of partially purified ADA1 and ADA2 were determined by using various concentrations of EHNA in the presence of adenosine substrate. Each point represents the mean of triplicate determinations (standard deviation, <5%).

was synthesized from L-rhamnose by the method of Bastian et al. (1). Partially purified ADA1 and ADA2 from human serum were kindly supplied by Maruho Co. Ltd. (Osaka, Japan).

Patients and serum samples. Serum samples from 49 patients with ATL, including 18 patients with the acute type, 6 patients with the lymphoma type, 20 patients with the chronic type, and 5 patients with the smoldering type, were kindly supplied by Ryukyu University Hospital (Okinawa, Japan), Nichinan Hospital (Miyazaki, Japan), and Nagasaki University Hospital (Nagasaki, Japan) for the present studies. Serum samples from 12 patients with HAM and 148 healthy HTLV-1 carriers were also provided by the same institutions mentioned above. Serum samples from 223 healthy individuals were used as controls. The age distribution of all subjects was 30 to 80 years, with 226 males and 210 females. All serum samples were stored at −80°C immediately after separation from peripheral blood prior to analysis.

Sera from 46 patients with AIDS (all males), 179 homosexual males (including 140 who were positive for HIV-1 antibody), and 37 heterosexual males, which served as controls, were obtained at the Veterans Affairs West Side Medical Center. The age distribution was 20 to 60 years.

Isolation of lymphocytes. Peripheral blood mononuclear cells (PBMCs) from healthy blood donors were separated by Ficoll-Paque (Pharmacia LKB Biotechnology Inc., Uppsala, Sweden) density gradient centrifugation. PBMCs (2×10^6/ml) were distributed into 24-well flat-bottom microtiter plates (Sumitomo Bakelite Co., Ltd., Tokyo, Japan) and were cultured in RPMI 1640 medium (GIBCO Laboratories, Grand Island, N.Y.) supplemented with 10% of heat-inactivated fetal calf serum (General Scientific Laboratories, Los Angeles, Calif.), 10 mM HEPES (*N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid), 100 U of penicillin per ml, and 100 μg of streptomycin per ml.

T-cell lines. The T-cell lines used in the present study were H-9 cells from a patient with T-cell lymphoma; HPB-ALL cells and MOLT-4 cells from a patient with acute lymphoblastic leukemia (11); MT-2 and SALT-3 cells (21), which are HTLV-1-infected cell lines; and H-9IIIB and MOLT-4 IIIB cells, which are HIV-1-infected cell lines. Cell-free supernatants were harvested from these cell cultures and were stored at −80°C prior to the tests for ADA isoenzyme levels.

Enzyme assay. The ADA activity was assayed by a modification of the kinetic method described by Ellis et al. (4) with a model 7070 type Automatic Analyzer (Hitachi Co. Ltd., Tokyo, Japan). One enzyme unit is the amount of enzyme that converts 1 μM adenosine to inosine and ammonia per min at 37°C.

ADA1 and ADA2 activities were determined by Muraoka et al. (12) with various concentrations of EHNA in the presence of adenosine substrate. ADA2 activity and total ADA activity were measured in the presence or absence of 100 μM EHNA (19). We also examined the effects of serum components on the specific inhibition of the ADA1 isoenzyme at 100 μM EHNA by adding increasing amounts of partially purified ADA1 and ADA2, respectively, to a normal serum sample and assaying before and after the addition of EHNA. No interference in the inhibition of ADA1 was detected (96% inhibition), and more than 95% of the total ADA2 activity was recovered (Fig. 1). ADA1 activity can therefore be calculated by subtracting the residual activity in the presence of 100 μM EHNA (ADA2) from total ADA activity.

Statistical analysis. The statistical significance of the results was calculated by using an unpaired Student's *t* test, with $P < 0.05$ accepted as significant.

TABLE 1. ADA isoenzyme activities in sera of patients with HTLV-1-associated diseases

Group	No. of subjects	Mean ± SD (range) activity (units/liter)	
		ADA1	ADA2
ATL	49	14.9 ± 19.1[a] (5.0–94.5)	25.6 ± 13.3[a] (8.0–62.9)
HAM	12	5.9 ± 2.3[a] (2.7–6.1)	20.6 ± 6.9[a] (10.4–26.4)
Carriers	148	4.1 ± 1.7[a] (3.9–7.9)	16.4 ± 6.5[a] (9.0–37.7)
Controls	223	2.6 ± 1.3 (0.3–7.2)	10.4 ± 2.9 (4.9–17.8)

[a] A significant difference ($P < 0.001$) was shown in comparison with the results for the controls.

RESULTS

ADA isoenzyme levels in sera of patients with HTLV-1 infection. ADA isoenzyme activities in the sera of subjects infected with HTLV-1 are given in Table 1. The ADA1 and ADA2 activities in the healthy HTLV-1 carriers and patients with HAM and ATL were significantly elevated compared with those in the sera of controls ($P < 0.001$). In particular, ADA1 activity was markedly increased in the sera of patients with ATL compared with that in the sera of patients ($P < 0.001$) with HAM and was slightly increased in the sera of patients with HAM compared with that in the sera of HTLV-1 carriers ($P < 0.001$). ADA2 activity in the sera of patients with ATL was significantly elevated compared with that in the sera of patients with HAM ($P < 0.001$) and was slightly increased in the sera of patients with HAM compared with that in the sera of HTLV-1 carriers ($P < 0.01$). The results clearly indicated that ADA1 activity was increased in the sera of patients with ATL.

The ADA isoenzyme activities in the sera of patients with ATL grouped according to the different forms of the disease are given in Table 2. ADA1 activities in the sera of subjects with the acute and lymphoma types of ATL were greater than those in the sera of subjects with the chronic and smoldering types ($P < 0.001$), and the activities in the sera of subjects with the acute type were shown to be greater than those in the sera of subjects with the lymphoma type ($P < 0.01$). No significant difference in ADA1 activity was noted in the sera of subjects with the chronic type compared with that in the sera of subjects with the smoldering type. The ADA2 activities in the subjects with the acute and lymphoma types were significantly elevated compared with those in the sera of subjects with the chronic type ($P < 0.01$) and were elevated in the sera of subjects with the chronic type compared with those in the sera of subjects with the smoldering type. These data indicate that ADA isoenzyme activities showed different patterns among subjects with the different subtypes of ATL.

ADA isoenzyme levels in sera of patients with HIV-1 infection. ADA isoenzyme activities in the sera of AIDS patients,

TABLE 2. ADA isoenzyme activities in sera of patients with different ATL subtypes

ATL subtype	No. of subjects	Mean ± SD (range) activity (units/liter)	
		ADA1	ADA2
Acute	18	28.2 ± 26.1[a] (18.4–94.5)	28.4 ± 15.8[a] (8.0–62.9)
Lymphoma	6	12.8 ± 5.9[a] (5.6–20.5)	31.9 ± 13.1[a] (15.4–50.8)
Chronic	20	5.9 ± 4.9 (3.6–8.2)	23.9 ± 11.1[a] (16.9–61.5)
Smoldering	5	5.6 ± 1.8 (5.0–7.9)	14.3 ± 0.7 (13.0–15.0)

[a] Significant difference ($P < 0.001$) in comparison with the results for patients with the smoldering type of ATL.

TABLE 3. ADA isoenzyme activities in sera of AIDS patients and HIV-1 carriers

Group	No. of subjects	Mean ± SD (range) activity (units/liter)	
		ADA1	ADA2
AIDS	46	6.5 ± 3.4[a] (3.3–13.8)	28.1 ± 7.0[a] (13.6–48.2)
HIV-1 positive	140	5.8 ± 2.1[a] (2.2–13.5)	23.3 ± 8.2[a] (12.4–34.2)
HIV-1 negative	39	2.8 ± 1.5 (1.1–6.9)	11.2 ± 3.8 (4.6–13.3)
Healthy heterosexual males[b]	37	2.5 ± 1.1 (1.8–5.8)	9.2 ± 6.1 (5.0–18.7)

[a] Significant difference ($P < 0.001$) in comparison with results for heterosexual males.
[b] Non-HIV-1-infected individuals, used as controls.

homosexual males (HIV-1 antibody-positive and -negative individuals), and healthy heterosexual males are given in Table 3. ADA1 and ADA2 activities in the sera of subjects with AIDS and HIV-1 antibody-positive individuals were significantly elevated compared with those in the sera of heterosexual males ($P < 0.001$). No significant difference in ADA isoenzyme activities in the sera of HIV-1 antibody-negative individuals compared with that in the sera of the controls was found. In particular, ADA2 activity in the sera of AIDS patients was significantly elevated compared with that in the sera of HIV-1 antibody-positive individuals ($P < 0.01$), whereas there was no significant difference in ADA1 activity between these two subjects.

ADA isoenzyme levels in cultured T-cell lines. To determine the levels of ADA isoenzymes in the T-cell lines including HTLV-1- and HIV-1-infected cells, the culture supernatants were assayed (Table 4). The ADA isoenzyme levels in various cell lines were increased compared with those in the control cells (PBMCs). Markedly increased ADA1 activity was found in MOLT-4 and HPB-ALL cells compared with that in HTLV-1- and HIV-1-infected cells ($P < 0.01$). The ADA1 levels in the human T-cell lines, including CCRF-CEM, RPMI-8402, and HPB-ALL cells, were higher compared with those in MOLT-4 and MT-2 cells (data not shown). In contrast, ADA2 activities in both HTLV-1 and HIV-1-infected cells were found to be increased in comparison with those in H-9, MOLT-4, and HPB-ALL cells ($P < 0.01$), and the ADA2 activity in HIV-1-infected cells was greater than that in HTLV-1-infected cells ($P < 0.01$).

TABLE 4. ADA isoenzyme activities in cultured T cell lines[a]

Cell line	Activity (units/10^6 cells)	
	ADA1	ADA2
Control	1.1	3.7
H-9	10.7	6.7
MOLT-4	24.5	4.0
HPB-ALL	22.6	6.6
MT-2	3.8	12.3
SALT-3	8.8	9.4
H-9IIIB	6.7[b]	20.6[b]
MOLT-4IIIB	10.4[b]	29.8[b]

[a] Human T-cell lines, including H-9, MOLT-4 and HPB-ALL cells, HTLV-1-infected cell lines (MT-2 and SALT-3 cells), and HIV-1-infected cell lines (H-9IIIB and MOLT-4IIIB cells), were cultured in RPMI 1640 medium. PBMCs were also cultured as controls under the same conditions used for the various cell lines. The culture supernatants were harvested after centrifugation of the various cells at 250 × *g* for 10 min for measurement of ADA isoenzyme levels. Values are means and were determined from triplicate samples (standard deviations, <10%).
[b] Significant difference ($P < 0.01$) in comparison with ADA isoenzyme levels in H-9 or MOLT-4 cells.

ADA isoenzyme activities in cultured MOLT-4 cells with HIV-1 infection. To investigate further the ADA isoenzyme levels in MOLT-4 cells with HIV-1 infection, the supernatants of MOLT-4 and MOLT-4IIIB cells in coculture (MOLT-4–MOLT-4IIIB cells) were analyzed. A cytopathogenic ballooning of the MOLT-4–MOLT-4IIIB cells was observed 4 h after the beginning of culture, with an increase in the number of giant cells that appeared following incubation, whereas no giant cell formation was observed in the MOLT-4 cell culture. ADA1 and ADA2 activities in the culture supernatants of the MOLT-4–MOLT-4IIIB cells were greater on the third and the fifth days during culture compared with those in MOLT-4 and MOLT-4IIIB cells (Fig. 2). In particular, markedly increased ADA1 activity was observed in the MOLT-4–MOLT-4IIIB cells when the giant cells were formed, whereas ADA2 activity was slightly increased compared with those in the MOLT-4 and MOLT-4IIIB cells. In addition, ADA2 activity in MOLT-4IIIB cells increased compared with that in MOLT-4 cells, whereas ADA1 activity in MOLT-4 cells was greater than that in MOLT-4IIIB cells.

DISCUSSION

ADA is a catabolic enzyme of the nucleotides involved in purine metabolism, and aminohydrase catalyzes the deamination of adenosine and deoxyadenosine. ADA activity was found to be increased in immature T lymphocytes; this was followed by decreased ADA activity with advancing cell maturation (27). It has also been reported that the ADA activity of T-cell lines measured throughout the stages of differentiation was the greatest in undifferentiated T lymphocytes (26). The difference in the enzyme levels found in the leukemic cells was due to the difference in cell metabolism, which is similar to the factors that cause high levels of ADA activity in the T-cell line (3, 28).

It has been reported that the ADA activity in serum is greater in patients with ATL (14) and AIDS (22), and the ADA activity in the sera of patients with the acute type of ATL was also greater than that in the sera of patients with the chronic type of ATL. In our previous studies, ADA activity was also confirmed to be higher in the sera of patients with ATL and AIDS. ADA isoenzymes consist of three groups (ADA1, ADA2, and ADA1+cp) with different molecular weights, kinetic properties, and distributions in tissue. In contrast to ADA1, which has been studied extensively, relatively little information is available for ADA2, although ADA2 is a major component of human serum. Therefore, qualitative detection of both ADA1 and ADA2 enzymatic activities in serum may be associated with retroviral infectious diseases.

In the study described here, we demonstrated that ADA1 activity is greater in the sera of patients with the acute and lymphoma types of ATL compared with that in the sera of patients with the chronic and smoldering types. A significant increase in ADA2 activity was observed in the sera of patients with the acute, lymphoma, and chronic types of ATL compared with that in the sera of patients with the smoldering type of ATL and HTLV-1 carriers. In clinical studies of ATL, increased ADA isoenzyme levels were found in the following order: healthy HTLV-1 carriers < smoldering ATL < chronic ATL < lymphoma ATL and acute ATL. The results therefore suggested that the ADA1 level generally reflects the activity

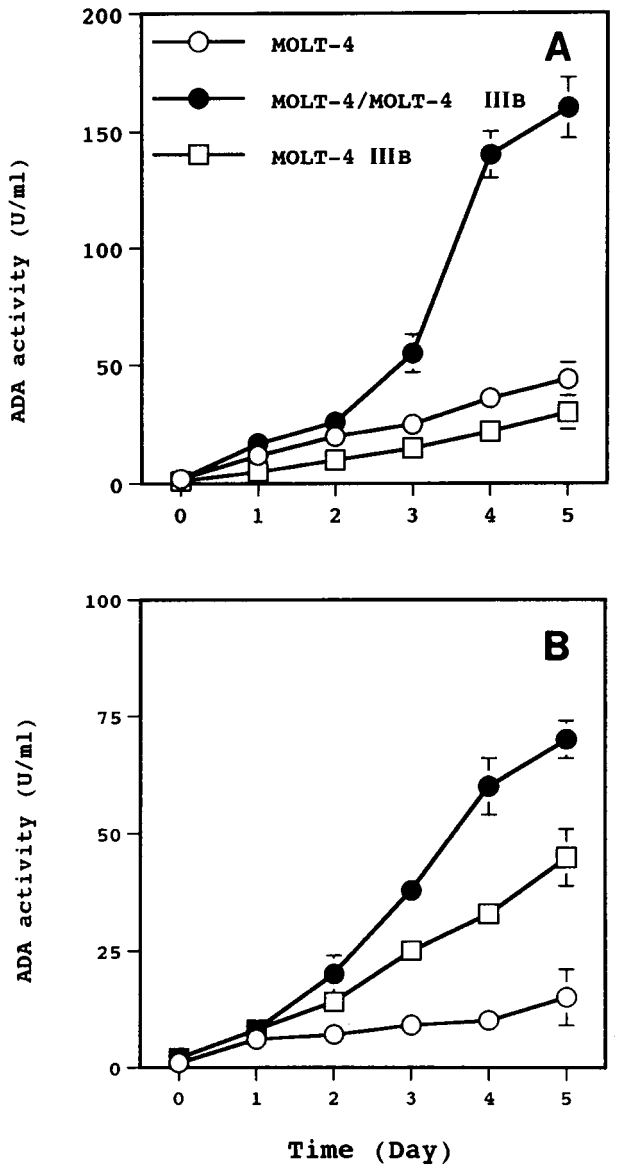

FIG. 2. ADA isoenzyme activities in culture supernatants of MOLT-4 cells infected with HIV-1. ADA1 (A) and ADA2 (B) activities in MOLT-4, MOLT-4IIIB, and cocultured MOLT-4–MOLT-4IIIB cells are shown. Each point represents the mean ± standard deviation of triplicate determinations. MOLT-4 cells were incubated in the presence of 2 μg of polybrane per ml at 37°C for 30 min, and a concentration of 2×10^6 cells per ml was mixed with 1×10^6 cells per ml (MOLT-4IIIB cells infected with HIV-1). The mixtures were cultured in RPMI 1640 medium, and ADA isoenzyme levels in the culture supernatants were measured up to the fifth day of the experiment.

seen in the acute stage of disease and that the higher ADA2 level is closely associated with the chronic stage of the disease.

The membrane surface antigen of ATL cells in the peripheral blood of patients showed characteristics of helper inducer T-cell subsets with $CD3^+$ $CD4^+$ $CD8^-$ $CD25^+$ markers (6). $CD25^+$ was also expressed on $CD4^+$ lymphocytes of HTLV-1 carriers to a significantly greater extent than it was on the lymphocytes of healthy controls (29). ATL cells are malignant and are transformed by HTLV-1 infection, and the infected cells eventually promote the increased level of ADA activity by cell activation.

ADA isoenzyme activity in the sera of the AIDS patients and HIV-1 antibody-positive homosexual males were found to be higher than that in the sera the HIV-1 antibody-negative homosexual males. In addition, ADA2 activity was markedly increased in the sera of AIDS patients compared with that in the sera of HIV-1 antibody-positive individuals. It has been shown that interleukin-2 production in the lymphocytes of AIDS patients was found to be lower, while the expression of the interleukin-2 receptor was higher after stimulation with phytohemagglutinin (9). In addition, ADA activity in lymphocytes from patients with AIDS-related complex was reported to be greater after mitogen stimulation since it is known that ADA activity in the culture supernatants of mitogen-stimulated PBMCs from healthy donors was greater than that seen in the culture supernatants of PBMCs not stimulated with mitogen (13). These results suggest that the ADA activity in infected cells is seemingly promoted by HIV-1 infection. Furthermore, increased ADA1 and ADA2 activities in the culture supernatants of HIV-1-infected MOLT-4 cells were demonstrated. The results provide evidence for the increased production of ADA isoenzymes by cells infected with HIV-1.

Ratech et al. (18) reported that ADA2 activity was increased exclusively in nonlymphoid cells, while ADA1 activity was found in both lymphoid and nonlymphoid cell types. In the present study, ADA1 activity was observed to be markedly increased in both MOLT-4 and HPB-ALL cells compared with ADA2 activity. However, ADA2 activity in both HTLV-1 and HIV-1-infected cells (MT-2, H-9IIIB, and MOLT-4IIIB cells) was demonstrated to be constitutively higher. These results suggest that the increase in ADA1 and ADA2 activities in the culture supernatants of retrovirus-infected cells is due to a change in the regulation of cell metabolism and that the increase in ADA1 and ADA2 activities in serum may be caused by HTLV-1 infection and HIV-1 infection, respectively.

It was recently suggested that ADA may be directly involved in T-cell activation through its interaction with the CD26 cell surface marker (8), which is a T-cell activation molecule and which has a biological function identical to that of dipeptidyl peptidase IV (7). T-cell activation through the CD26 molecule has also been shown to mediate interleukin-2 production and the proliferation of $CD4^+$ cells (16). It was shown that the number of $CD26^+$ cells is decreased in asymptomatic HIV-1-seropositive individuals before $CD4^+$ cell depletion occurs (2).

In conclusion, the present study indicated that ADA isoenzyme levels are differentially expressed in the sera of patients with retrovirus infections associated with ATL or AIDS. The levels of ADA isoenzyme activities in the sera of patients with T-cell leukemia with myelopathy, HTLV-1-infected carriers, HIV-1-positive carriers, and patients with AIDS were shown to be significantly higher than those in the sera of healthy controls. We demonstrated that the magnitude of the elevation in ADA isoenzyme levels in serum correlates well with the clinical conditions of the patients with the diseases caused by these retroviruses. Understanding of the causes of these diseases and the complex underlying immunodynamics and immunomodulation could be important for elucidating the mechanism of the increase in ADA isoenzyme activities in the lymphocytes and sera of patients infected with HTLV-1 and HIV-1, respectively.

ACKNOWLEDGMENTS

We thank Koichi Araki, Ryukyu University School of Medicine; Toshimitsu Shingu, Nichinan Hospital; and Michito Ichimaru and Shuichi Ikeda, Nagasaki University School of Medicine, for supplying serum samples for the present study. We also acknowledge the staff members of the Veterans Affairs West Side Medical Center for their technical assistance with the assay.

This work was funded by Maruho Co., Ltd., and in part by a grant from the University of Illinois at Chicago (to David W. Ou).

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